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Relationship of Event-Related Brain Potentials and Lead Absorption A Review of Current Evidence

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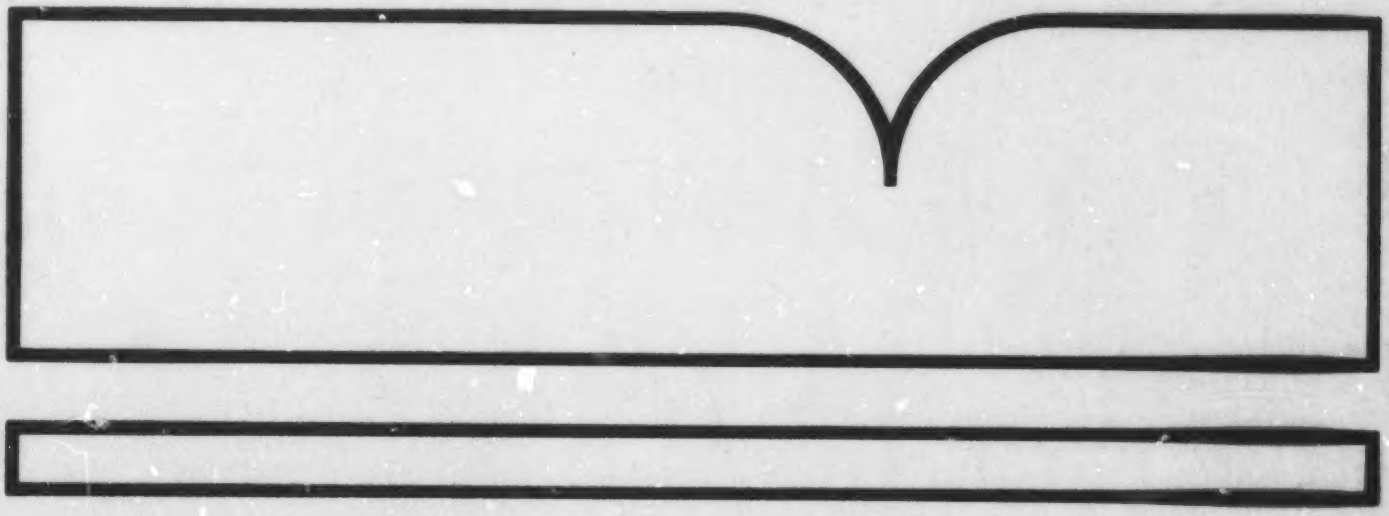

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THE RELATIONSHIP OF EVENT-RELATED BRAIN POTENTIALS AND LEAD ABSORPTION: A REVIEW OF CURRENT EVIDENCE[1]

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16. ABSTRACT

The results of human and animal studies of the effects of lead absorption on sensory evoked and slow brain potentials are reviewed. These studies of flash evoked potentials in rats produced conflicting evidence of increased and decreased latencies, decreased amplitude, and increased or decreased cortical excitability. Studies of slow wave voltage in children during sensory conditioning indicated a linear relationship to blood lead level in two studies, an effect that could not be replicated in an independent sample of children. Results of a fourth study indicated that slow voltage measures were more sensitive to lead during active rather than passive conditioning. Conflicting evidence of lead effects on pattern-reversal visual evoked potentials in children was found in three studies. Evidence of increased latencies of brainstem auditory evoked potentials at blood lead levels above 25 /dl were reported in two studies. Sensory evoked potentials hold considerable promise as noninvasive, clinically valid, culture free measures of the effects of lead exposure on sensory nerve conduction, but further study is needed in humans and animals to clarify inconsistencies in the limited existing literature.

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Sensory evoked and slow brain potentials, collectively known as event-related potentials (ERPs), have been used during the past decade to study the effects of lead exposure on central nervous system function in humans and animals. The objectives of this paper are to review these studies, to consider the health implications of these data, and to suggest future directions for neurobehavioral studies of lead effects in humans.

ANIMAL STUDIES

The effects of lead exposure on flash evoked potentials (FEP) in rats have been studied by Fox et al (1977, 1979), Feeney et al (1979) and Winneke (1979). Important methodological details and results of these studies are summarized in Table I. Although lead-related changes in FEP latency or amplitude were observed in each of these studies, the pattern of effects was inconsistent across studies. For instance, Fox et al (1977) reported increased latencies (components P1, N1, P2, N2), Feeney et al reported decreased (P2) latency, and Winneke found no latency change in Pb-exposed animals compared to controls. Winneke, on the other hand, observed depressed FEP amplitudes, while Fox et al (1979) observed increased amplitude recovery (cortical excitability) to paired flashes in Pb-exposed rats relative to controls.

A further puzzling inconsistency exists in the reports of Fox et al (1977 vs. 1979). The effect of Pb exposure on the recovery function of visual cortex was evaluated in both studies -- apparently in the same animals. Fox et al (1977) reported decreased CNS recovery based on latency measures, while Fox et al (1979) reported increased CNS recovery (excitability) based on amplitude measures in Pb-exposed animals compared to controls. The authors make no effort to reconcile these clearly discrepant findings.

Inconsistent PEP findings could be due to a variety of methodological differences among studies. The doses, duration of maternal and offspring exposure, age at testing, species or strains of rats, and electrophysiological testing methods varied considerably among investigators. Results of these studies do suggest, however, that neonatal Pb exposure produced persistent effects on visual system function in adult rats.

HUMAN STUDIES

During the past eight years a series of collaborative studies by the University of North Carolina and the U.S. Environmental Protection Agency have been undertaken to explore the effects of asymptomatic lead exposure on neurobehavioral function in children. Three evaluations were made of one group of children including an initial assessment in 1978-79 (Otto et al 1981), a two-year follow-up in 1980 (Otto et al 1982), and a five-year follow-up in 1983 (Otto et al 1985, Schroeder et al, 1985). A replication study in an independent group of children was completed in 1984 (Hawk et al 1985; Robinson et al 1985). The electrophysiological results of these studies will be reviewed below.

Two primary sources of exposure were identified in the original study group: (1) lead-contaminated dust transmitted into homes on the clothing of workers from a battery manufacturing plant; and (2) lead-based paint prevalent in homes built prior to 1950. It should be noted that the soil around homes with lead-based exterior paint may be contaminated from weathering even in the absence of peeling paint. The primary source of exposure in the replication study was lead-based paint. The primary route of exposure in all cases was ingestion.

higher than in the replication group due to employment in the battery plant. Almost all parents of children in the second group were unemployed (Hollingshead Class V). Children ranged in age from 1 to 6 years in the initial evaluation, 3 to 7 years at two-year follow-up, 6 to 12 years at five-year follow-up, and 3 to 7 in the replication study. See Milar et al (1980) and Hawk et al (1985) for additional demographic details.

Table II summarizes the exposure, medical, psychometric, and demographic measures obtained from children and parents in this series of studies. Children with any acute illness, history of perinatal trauma, iron deficiency neurological disorder, or frank mental retardation (IQ < 60) were excluded from data analyses. Socio-economic status, H.O.M.E. scores, maternal IQ, age and gender were used as covariates or control variables in statistical analyses of electrophysiological data.

Several different electrophysiological tests were used in these studies: sensory conditioning (active and passive), pattern-reversal visual evoked potential (PREP), and brainstem auditory evoked potential (BAEP). Methodological details of these tests are provided in Otto et al (1985). The only test used in all evaluations was passive sensory conditioning. Active sensory conditioning was used only in the five-year follow-up study because children under five years of age do not button press reliably. The PREP and BAEP were used in the five-year follow-up and replication studies. Results of these tests will be reviewed and discussed below.

Slow wave voltage during sensory conditioning. Electrical activity of the brain was recorded from the vertex of children while they watched silent cartoons. A warning tone was presented at random intervals signalling that the cartoon would be interrupted briefly. This test

is a form of classical conditioning in which the warning tone is a conditional stimulus (CS) which is paired with a mildly aversive unconditional stimulus (UCS), the cartoon interruption. Electrical activity (slow wave voltage) was recorded during the CS-UCS interval and averaged across successive trials (1-35 in the initial evaluation; 1-50 and 50-100 in later evaluations).

Slow wave voltage during the CS-UCS interval is assumed to be an electrophysiological correlate of conditioning -- i.e., the child learns to anticipate that the cartoon will be interrupted when the warning signal is presented. In the passive test, however, there is no behavioral measure of conditioning to validate this inference. The functional significance of this measure of slow wave voltage, therefore, remains uncertain in the passive test.

Results of sensory conditioning tests in this series of studies are summarized in Table III. The initial evaluation (Otto et al, 1981) indicated that slow wave voltage varied as a linear function of blood lead (PbB) level and that the slope of this function varied with age as shown in Figure 1. Results of the two-year follow-up study showed a similar age x PbB interaction of slow wave voltage during passive sensory conditioning (Otto et al, 1982). Slow wave voltage during passive conditioning, however, did not vary with PbB at five-year follow-up.

Because the children were old enough (6-12 years) to button press reliably at five-year follow-up, an active form of the sensory conditioning test was added to the electrophysiological battery. Children were asked to press a button as quickly as possible when the cartoon was interrupted. The button press immediately restored the cartoon enabling children to control the duration of the interruption.

Figure 2 illustrates waveforms from the active and passive tests. Slow wave voltage (negativity) during the CS-UCS interval was much greater during active than passive conditioning. The active test thus elicits a more robust electrophysiological response than the passive test. Slow wave negativity during active conditioning, moreover, increased linearly with PbB levels of children obtained at five-year follow-up (Otto et al, 1985). Therefore, the active test also appears to be more sensitive than the passive test to the effects of lead exposure in children.

In the replication study we were constrained to used the passive form of the sensory conditioning test because many of the children were considered to be too young (three and four years old) to button press reliably. No significant relationship of slow wave voltage and PbB levels were found in this study. We thus failed to replicate previous findings (Otto, et al 1981, 1982) in a different group of children. Inconsistent findings among the four studies may result from several factors. (1) Results of the five-year follow-up study (Otto et al, 1985) indicate that the passive test is not particularly sensitive to lead exposure in older children. Inconsistent findings may thus be due to the relative insensitivity of the passive test. (2) Different types of exposures in the two groups of subjects (e.g. secondary occupational exposure vs Pb-based paint) may produce different neurobehavioral consequences. (3) Methodological differences in data analysis between early (Otto et al, 1981, 1982) and later studies may have influenced findings. Stricter criteria for accepting single trials in slow wave averages were used in earlier studies. More eye movement artifact was tolerated in the five-year follow-up and replication studies to increase the number of trials in averages for individual children. More trials in averages result in

better reduction of noise from unrelated electrical activity of the brain. (4) Previous findings may have been Type I statistical errors-- i.e., slow wave voltage during passive conditioning may not be affected by low-to-moderate Pb exposure. Observation of a linear relationship of Pb and slow wave negativity during active conditioning (Otto et al, 1985), however, argues against this possibility.

Pattern reversal visual evoked potentials. In view of the reported effects of neonatal Pb exposure on visual evoked potentials in rats, reviewed above, pattern-reversal visual evoked potentials were added to the electrophysiological test battery in the five-year follow-up and replication studies. Although flash evoked potentials were used in animal studies, the pattern-reversal test was selected for pediatric assessment because the PREP has proven to be more sensitive than the FEP in most human testing applications (cf. Halliday and McDonald, 1981).

P1 latency has been found to be the most useful clinical parameter of the PREP. P1 latency is delayed in cases of optic neuritis (Halliday et al, 1972) and multiple sclerosis (Halliday et al, 1973). We predicted, therefore, that P1 latency would vary directly with blood lead levels, but this measure did not vary with PbB levels in either the five-year follow-up or replication study. Several other PREP measures varied with Pb exposure histories of children, however, as shown in figure 3. N1P1 amplitude increased (fig 3a) and N2 latency decreased (fig. 3b) in the five-year follow-up study (Otto et al, 1985). P1N2 amplitude (fig 3c) decreased with increasing Pb exposure history in the replication study.

These findings are problematic for several reasons. (1) Results of the two studies are inconsistent -- i.e., N1P1 vs. P1N2 amplitudes. (2) Results of the five-year follow-up study were contrary to prediction. We

hypothesized that undue Pb absorption should produce effects analogous to non-specific demyelinating disease -- namely, increased latency and decreased amplitude. (The observed relationship of P1N1 amplitude and PbB in the replication study, therefore, was consistent with predictions). (3) From a statistical point of view, the findings are weak. The multivariate test for the set of PREP measures in both studies was not significant, although exploratory univariate tests of certain parameters were significant at the .05 level of confidence.

Shorgia et al (1983) and Winneke et al (1984) have also used PREPs in evaluating the effects of Pb exposure in humans. Shorgia et al reported increased P1 component latencies in Pb workers compared to controls, but Winneke et al found that P1 latency in children decreased with increasing PbB within a range of 4 to 23 µg/dl. The mean PbB level of Pb workers in the Shorgia et al study was 62.5 µg/dl. It is possible that Pb has a biphasic effect on nerve conduction velocity (NCV), facilitating NCV at low concentrations, but slowing NCV at moderate to high concentrations. Results of lead studies using PREP measures are summarized in Table IV.

Although we failed to find effects of Pb exposure on P1 latency as predicted and as reported by Winneke et al, the pattern-reversal findings of the Nordenham study and five-year follow-up study are consistent. PREP latencies deceased with increasing PbB levels in both studies. The range of PbB levels at the time of PREP testing in the Nordenham (4-23 µg/dl) and five-year follow-up (6-30 µg/dl) studies may be a critical factor. The range of current PbB levels in the replication (6-47 µg/dl) and Shorgia et al (pb-worker mean PbB was 62.5 µg/dl) studies was considerably greater. Further research is needed to clarify the inconsistent findings concerning the effect of Pb exposure on visual evoked potentials in both

humans and animals.

Hearing and Brainstem auditory evoked potentials. Little evidence concerning the effect of Pb absorption on hearing or auditory evoked potentials in children is presently available. Auditory processing deficits have been reported in cases of Pb poisoning (Jenkins & Mellins, 1957) and asymptomatic exposure (Perino & Ernhart, 1974; Needleman et al, 1979). Geurit et al (1981) reported that BAEPs were not affected by Pb exposure in children living near a Pb smelter, although the lack of detail in that report precludes drawing any conclusions. We therefore conducted a limited audiometric screening of hearing threshold (using a 2 KHz pure tone) and recorded binaural BAEPs in the five-year follow-up and replication studies. Results of these studies are summarized in Table V.

BAEP results of the five-year follow-up and replication studies are shown in figure 4. Results of the former study were staight-forward: the latencies of BAEP waves III and V increased directly with PbB histories of children (fig. 4b). Results of the replication study were more complex and only partially consistent with earlier findings. Two KHz hearing thresholds increased significantly with PbB (fig. 4a) as did I-V interpeak latency (an index of central transmission time in the auditory pathway) (fig. 4c). Other parameters of the BAEP, however, exhibited a curvilinear relationship to Pb exposure history. Latencies of waves III, V and inter-peak latency I-III decreased from 6-25 µg/dl, but increased at PbB levels above 25 µg/dl (figure 4c).

Results of the two studies are consistent for Pb exposure histories above 25 µg/dl: BAEP latencies increase directly with the maximal PbB values found in the children's medical records. The curvilinear functions of BAEP latencies in the replication study suggest, however, a possible biphasic effect of Pb exposure on nerve conduction velocity in

the auditory pathway with facilitation at PbB levels below 25 ug/dl and slowing at PbB levels above 25 ug/dl.

Perhaps the most intriguing finding from the replication study was the significant increase in hearing threshold with increasing Pb exposure history. This finding suggests that Pb exposure impairs hearing and the peripheral segment of the auditory pathway. This preliminary finding is of considerable interest in view of the well-documented association of childhood lead poisoning, mental retardation and subtle learning disabilities (cf. USEPA, 1977). A selective hearing loss occurring in early childhood that remains undetected could result in speech pathology and learning impairment as the child grows. Such problems frequently are not identified until the child reaches school age and demonstrates performance deficiencies.

Recent confirmation of the effect of lead absorption on hearing thresholds has been found in the NHANES II study (Schwartz and Otto, in preparation). Audiometric testing of 5000 young people aged 4 to 19 years old was performed with pure tones at 500, 1000, 2000 and 4000 Hz. Hearing thresholds increased significantly with PbB level at the three lowest frequencies tested.

BAEP findings, moreover, suggest that Pb exposure affects central as well as peripheral segments of the auditory pathway. The adjustment of click intensity to obtain equal sensation levels in children tested in both studies does not permit us to verify the apparent hearing threshold effect using wave I latency because wave I latency varies with click intensity . In order to evaluate the validity and generality of our findings, a comprehensive audiometric, BAEP and speech assessment of an independent sample of children at risk for lead poisoning should be undertaken.

FUTURE DIRECTIONS IN NEUROBEHAVIORAL LEAD RESEARCH

1. Need for longitudinal studies. Evaluation of the neurobehavioral effects of lead exposure in humans, particularly psychometric data in children, has been hampered by the cross-sectional nature of most previous studies. Lead exposure history cannot be determined from a single blood lead measure, the most widely used metric of lead exposure in cross-sectional studies. Tooth lead measures provide an integrated measure of exposure history in children, but the limited availability of deciduous teeth and the analytic complexity of this measure limit its application. Longitudinal studies in which children or workers are sampled at regular intervals to document exposure history over an extended period of years offer the best solution. The Cincinnati Prospective Lead Project described elsewhere in this volume is an excellent example of the kind of longitudinal study needed to clarify the significance and persistence of behavioral and electrophysiological effects of Pb exposure reported in previous cross-sectional studies.

2. Need for comprehensive auditory assessment. Results of our recent studies (Otto, et al, 1985; Robinson, et al, 1985) suggest that lead exposure affects peripheral and central segments of the auditory pathway. Hearing thresholds and central conduction time were both altered in the replication study (Robinson, et al, 1985). The implications of subtle lead-related hearing loss in young children for subsequent speech and learning disorders were noted above. Audiometric evaluations are simple, standardized and fairly inexpensive to administer. BAEP testing is also fairly simple and standardized, though somewhat more expensive than audiometry. We recommend the addition of such tests to future pediatric lead studies and to lead worker monitoring programs.

Results of BAEP testing indicate that this electrophysiological measure is very sensitive to the effects of lead exposure. BAEP testing provides valuable information about central conduction in the auditory pathway, information that cannot be obtained from audiometric testing. Further BAEP studies in lead-exposed children and workers are needed, however, to clarify our previous findings. Does lead exposure really produce a biphasic dose-dependent effect on auditory function in children? Is the effect of lead on auditory function reversible? Are children more susceptible to lead-related hearing impairments than adults? Comprehensive audiometric, electrophysiological and speech assessments in children and adults are needed to resolve these questions.

3. Need for scotopic vision testing. Studies of visual evoked potentials in humans and animals all suggest lead-related alterations, although numerous inconsistencies were noted above. Further studies of visual function in humans and animals are needed to resolve these inconsistencies. Pattern-reversal visual evoked potentials, however, may not be a particularly sensitive measure to use. A series of *in vitro* (Fox & Sillman, 1979; Sillman et al, 1982; Tessier-Lavigne et al, 1985) and *in vivo* (Bushnell et al, 1977; Fox et al, 1985) animal studies suggest that rods are more susceptible than cones to Pb toxicity. That is, Pb affects night (scotopic) vision more than day (photopic) vision in animal models. If lead alters rod, more than cone function in humans, then PREPs are unlikely to show any consistent effect since the PREP reflects primarilly cone-mediated vision (Sokol, 1976). Tests of peripheral and dark-adapted vision in lead-exposed humans are needed to resolve this question.

4. Need for assessment of cognitive function. An area of considerable controversy has been the effect of lead absorption on cognitive development and intelligence in children (cf. contributions of Bornschein, Dietrich, Ernhart, Grant, McBride, Smith, Vimpani, Winneke and Yule in this volume). Interpretation of cross-sectional pediatric results has been clouded by the confounding effects of sociocultural variables. Recent work from our laboratory (Hawk et al, 1985) demonstrated an 18-point spead in full-scale Stanford-Binet IQ scores across the Pb exposure range (6-47 ug/dl) in three to seven year old children when socioeconomic status was controlled in the experimental design. We limited subjects to a subset of the U.S. population considered to be at highest risk for lead poisoning--i.e., low-income Black children fron SES classes IV and V on the Hollingshead Scale.

A parallel stategy of our group has been to use electrophysiological indices of sensory conditioning that are considered to be independent of standard IQ measures and to be free of the sociocultural biases of IQ tests. Early results (Otto et al, 1981; 1982) suggested that slow wave voltage measures obtained during sensory conditioning were sensitive to lead exposure in children and were uncorrelated with SES, maternal IQ, child IQ or Caldwell H.O.M.E. ratings of care-giving practices. As noted previously, slow wave voltage during passive conditioning did not vary with Pb exposure history in older children (Otto et al, 1985) or in an independent sample of three to seven year old children.

These inconsistent findings suggest the need for more sensitive and reliable electrophysiological measures of cognitive function in children. Preliminary results with a modified test indicate that the addition of a motor response improves the effectiveness of the sensory conditioning test markedly (Otto et al, 1985). Development of more sophisticated event-

related slow potential tests incorporating a P300 paradigm that is widely used in cognitive psychophysiology (cf. Donchin et al, 1978) is currently in progress. Courchesne et al (1983, 1985) have demonstrated the utility of such tests in normal and developmentally disordered children.

The clinical utility of event-related endogenous potentials has been most clearly demonstrated in studies of Alzheimer's disease and aging (Squires et al, 1980). The latency of the P300 wave, a positive ERP that peaks between 300 and 900 msec after presentation of an infrequent or meaningful stimulus, is delayed in patients with Alzheimer's disease relative to controls. P300 latency has been associated with stimulus evaluation time or "mental chronometry" (Kutas et al, 1977). P300 testing can be brief (10 to 20 minutes) and can be administered simply in standardized form with commercially available equipment. The application of P300 methods in neurotoxicity testing has been reviewed recently by Harbin (1985).

Although the effect of lead exposure on cognitive development has been studied extensively in children, studies of lead-exposed adults usually focus on peripheral nervous system function. Symptoms of acute lead poisoning in adults, however, include dullness, irritability, poor attention span, headaches, and loss of memory (reviewed in USEPA, 1985). The syndrome of lead encephalopathy in adults is well-known, but few efforts have been made to study the effects of asymptomatic lead exposure on cognitive function in adults. In view of increasing evidence that lead affects cognitive development in children at lower levels of exposure than previously thought (USEPA, 1985), further systematic study of cognitive function in lead-exposed adults is clearly needed. Classical neurobehavioral testing methods (e.g., Valciukas et al, 1978), computerized behavioral

test batteries (e.g., Baker et al, 1985) or endogenous ERP methods noted above would be appropriate for such studies.

SUMMARY

Sensory evoked and slow brain potentials have been used to study the effects of lead absorption on CNS function in both humans and animals. Results of these studies were reviewed and suggestions for future neurobehavioral lead studies were made. Although the results of individual studies suggest that these measures are very sensitive to the effects of lead absorption, many inconsistencies among studies were noted, particularly with regard to visual evoked potentials. The pattern-reversal VEP, which reflects primarily foveal vision, may be an inappropriate measure of lead effects if rods are more vulnerable than cones to exposure. Failure to replicate earlier reports of the relationship of slow wave voltage and lead exposure suggests that the passive sensory conditioning test is not a particularly sensitive measure of lead effects in children. Increased auditory brainstem EP latencies with blood lead levels above 25 µv/dl were reported in two pediatric studies. Further studies of sensory evoked and slow potentials in lead-exposed animals and humans are needed to clarify and extend the promising, but limited evidence presently available.

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TABLE I. EFFECTS OF NEONATAL LEAD EXPOSURE ON FLASH EVOKED POTENTIALS (FEP) IN RATS

STUDY	SPECIES/NUMBER OF ANIMALS	EXPOSURE INFORMATION	SIGNIFICANT RESULTS
Fox et al, 1977	Long-Evans (6 animals/treatment/age)	Newborn rats exposed to Pb via dam's milk; drinking water of dams contained 0.2% Pb acetate. Exposure ceased at weaning (21 days). Mean blood/brain Pb levels: Controls / Exposed — dy 21: 6/7 / 65/53 µg/dl; dy 90: 5/11 / 7/13	1. FEP latencies (P1,N1,P2,N2) were longer in Pb-exposed rats during development (days 9-13, 16, 20) and as adults (day 90). 2. Development of FEP components was delayed in Pb-exposed rats. 3. Latency recovery to paired flashes was decreased in Pb-exposed rats at 90 days. 4. Frequency-following response to repetitive flashes was decreased in Pb-exposed adult rats.
Fox et al, 1979	Long-Evans 6 controls 6 exposed	Same day-90 rats as above	Rats exposed neonatally to Pb showed increased cortical excitability (R2/R1 amplitude ratio of responses to paired flashes) compared to controls
Feeney et al, 1979	CD rats 9 controls 8 exposed	Newborn rats exposed to Pb via dam's milk, potential dams received 750 mg/kg Pb acetate dissolved in drinking water from day 21 until weaning of pups. No blood or Pb data provided for animals tested. PbB levels from duplicate sample exposed dams were 117 µg/dl at weaning vs. 4 µg/dl for control dams. Estimated PbB levels of all animals at testing was <4 µg/dl.	FEP latency (P2 only) in 70-80 day-old rats was shorter in Pb-exposed than control animals.

STUDY	SPECIES/NUMBER OF ANIMALS	EXPOSURE INFORMATION	RESULTS
Winneke (1979)	Wistar 10 animals/ treatment	For 60 days prior to mating: dams fed 4 diets: control, 750, 2260, or 6740 ppm Pb-acetate. Observed PbB levels in dams were: <5, 24, 53 and 87 µg/dl. PbB levels in offspring after 110-190 d of postnatal Pb-feeding: <5, 29, 40, and 64 µg/dl.	Rats were tested at 150-190 days of age. FEP amplitudes (N1,N1P2) were lower in two highest exposure groups than controls. Threshold effect level of 30-40 µg/d noted. No Pb-related latency effects found.

TABLE II. SUMMARY OF EVALUATIONS

I. Exposure Evaluation

- A. Fantus Lead Poisoning Questionnaire
- B. Blood Lead (PbB): Flameless Atomic Absorption Spectrometry
- C. Free Erythrocyte Protoporphyrin (FEP)

II. Medical Evaluation

- A. Medical History
- B. Pediatric Neurological Examination
- C. Growth: Height, Weight, Head Circumference
- D. Lab Tests: BDS, WBC, RBC, Hgb, HCT, MCV, MCH, MCHC

III. Electrophysiological Evaluation

- A. Slow Cortical Potentials during Sensory Conditioning
- B. Brainstem Auditory Evoked Potentials
- C. Pattern-Reversal Visual Evoked Potentials

IV. Psychometric-Behavioral Evaluation

- A. Stanford-Binet Intelligence Test-Revised (Children over 30 months)
- B. Bayley Scales of Mental Development (Children under 30 months)

V. Demographic Covariate Evaluation

- A. Maternal IQ: Ammons Quick Test or Peabody Picture Vocabulary Test Revised
- B. Socioeconomic Status: Hollingshead Two-Factor Index
- C. Quality of Caregiving Environment: Caldwell's Home Observation for Measurement of the Environment
- D. Chronological Age
- E. Sex

TABLE III. RELATIONSHIP OF SLOW WAVE VOLTAGE AND PbB LEVELS DURING SENSORY CONDITIONING

STUDY	NUMBER OF SUBJECTS IN DATA ANALYSIS	AGE (YEARS)	PbB AT TESTING (µg/dl)	TYPE OF CONDITIONING	RESULTS
INITIAL EVALUATION (Otto et al, 1981)	41	1-6	6-55	PASSIVE (35 trials)	SLOW WAVE VOLTAGE VARIED AS A LINEAR FUNCTION OF PbB AND AGE
2-YEAR FOLLOW-UP (Otto et al, 1982)	28	3-7	14-39	PASSIVE (100 trials)	SLOW WAVE VOLTAGE VARIED AS A LINEAR FUNCTION OF PbB AND AGE DURING LATE TRIALS (41-100) ONLY
5-YEAR FOLLOW-UP (Otto et al, 1985)	48	6-12	6-30	PASSIVE (100 trials) AND ACTIVE (50 trials)	SLOW WAVE VOLTAGE VARIED AS A LINEAR FUNCTION OF CURRENT PbB DURING ACTIVE, BUT NOT DURING PASSIVE CONDITIONING
REPLICATION STUDY (Otto et al, in preparation)	68	3-7	6-47	PASSIVE (100 trials)	SLOW WAVE VOLTAGE DID NOT VARY WITH PbB LEVELS OR AGE

TABLE IV. RELATIONSHIP OF PATTERN-REVERSAL VISUAL EVOKED POTENTIAL MEASURES AND PbB

STUDY	NUMBER OF SUBJECTS IN DATA ANALYSIS	AGE (YEARS)	PbB AT TESTING (µg/dl)	RESULTS
Shorgia et al (1983)	31 Exposed 37 Control	42	62.5 19.0	REPORTED INCREASED P1 LATENCIES IN Pb-WORKERS COMPARED TO CONTROLS
Winneke et al (1985)	122	6-7	4-23	REPORTED DECREASING P1 LATENCY WITH INCREASING PbB
5-Year Follow-up (Otto et al, 1985)	43	6-12	6-30	N1P1 AMPLITUDE INCREASED AND N2 LATENCY DECREASED WITH INCREASING ORIGINAL PbB
Replication Study	70	3-7	6-47	P1N2 AMPLITUDE DECREASED WITH INCREASING PbB (MAXIMAL = 6-56 µg/dl)

TABLE V. RELATIONSHIP OF BRAINSTEM AUDITORY EVOKED POTENTIAL MEASURES AND PbB IN CHILDREN

STUDY	NUMBER OF SUBJECTS IN DATA ANALYSIS	AGE (YEARS)	Pb (µg/dl) a. CURRENT b. MAXIMAL	RESULTS
5-YEAR FOLLOW-UP (Otto et al, 1985)	45	6-12	a. 6-30 b. 6-59	WAVE III AND V LATENCIES INCREASED LINEARLY WITH INCREASING MAXIMAL, BUT NOT CURRENT PbB
REPLICATION STUDY (Otto et al, in preparation)	65	3-7	a. 6-47 b. 6-56	(1) HEARING THRESHOLD INCREASED LINEARLY WITH PbB (CURRENT AND MAXIMAL). (2) WAVE I LATENCY DECREASED LINEARLY WITH PbB (CURRENT AND MAXIMAL). (3) WAVE III, V LATENCIES AND IPL I-III, I-V SHOWED CURVILINEAR RELATIONSHIP TO PbB (MAXIMAL ONLY). (4) IPL I-V INCREASED LINEARLY WITH PbB (MAXIMAL ONLY)

FIGURE LEGENDS

Figure 1. Interactive effects of age and blood lead levels on slow wave voltage in children during passive sensory conditioning. Predicted slow wave voltage and 95% confidence limits are depicted as a function of original blood lead levels at the extreme ages of subjects at initial evaluation. (Adapted from Electroenceph. Clin. Neurophysiol., 1981, 52: 235).

Figure 2. Summary averages of slow potentials observed at frontal (Fz), central (Cz) and parietal recording sites in children during active and passive sensory conditioning (five-year follow-up evaluation). The electro-oculogram (EOG) recorded from electrodes above and below the right eye is also shown. Horizontal bars above averages depict intervals during which conditioned (CS) and unconditioned (UCS) stimuli were presented. Slow wave measurement intervals (SW1 and SW2) are designated by vertical lines. Note that slow wave voltage is much greater during active than passive conditioning.

Figure 3. Scatter plots and regression lines for N1P1 amplitude (a), N2 latency (b) and P1N2 amplitude (c) of the pattern reversal visual evoked potential as a function of maximal blood lead levels of children. (a) and (b) were obtained from chidren aged 6 to 12 years in the five-year follow-up study. (c) was obtained from children aged 3 to 7 years in the replication study.

Figure 4. Scatter plots, regression lines, and 95% confidence limits of (a) hearing threshold, (b) BAEP wave V latencies of boys and girls in the five-year follow-up study, and (c) BAEP wave V and interpeak V-I latencies of children in the replication study as functions of maximal blood lead levels. Hearing thresholds were determined audiometrically using a 2 KHz pure tone in the replication study. A linear relationship of wave V latency and PbB was found in children aged 6 to 12 years (b), while a curvilinear relationship was found in children aged 3 to 7 years (c).

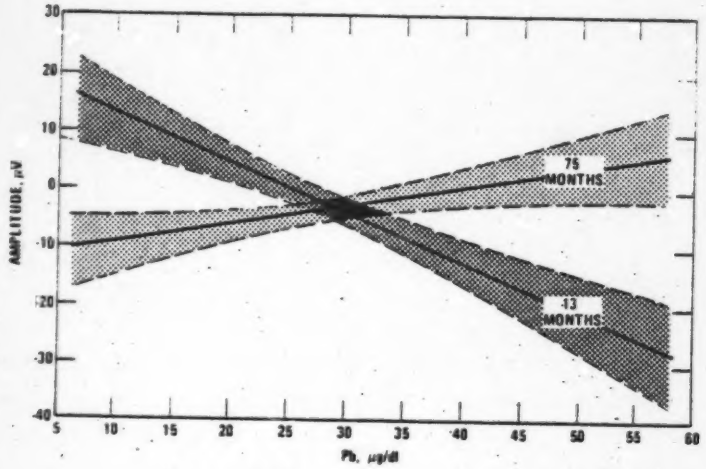

AMPLITUDE, μV
30
20
10
0
-10
-20
-30
-40
5
10
15
20
25
30
35
40
45
50
55
60
Pb, μg/dl
75 MONTHS
13 MONTHS

Fig. 1

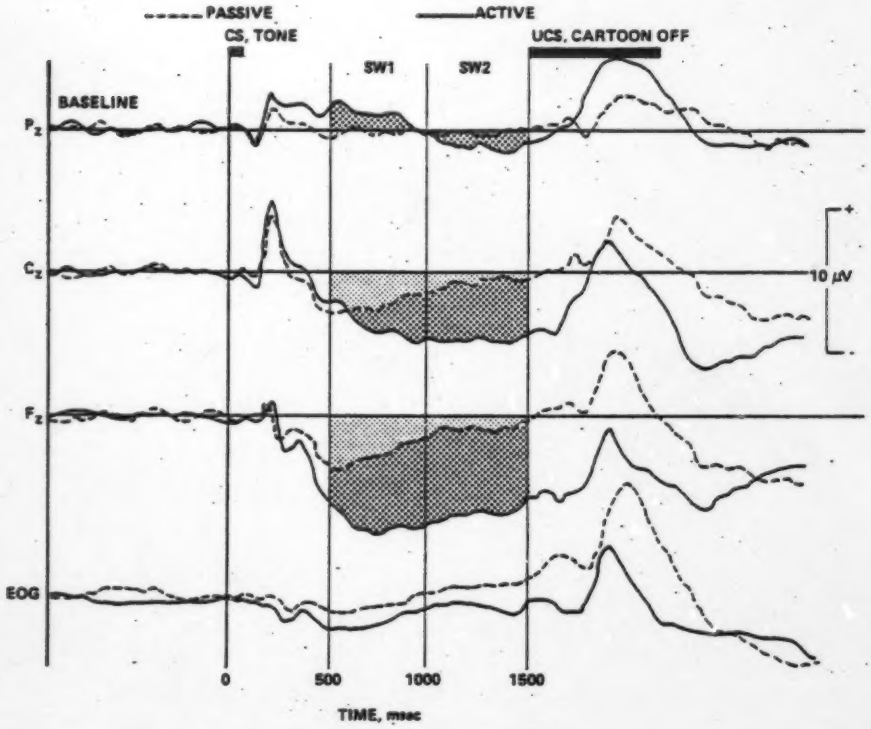

PASSIVE
ACTIVE
CS, TONE
UCS, CARTOON OFF
SW1
SW2
BASELINE
Pz
Cz
Fz
EOG
10 μV
+
0
500
1000
1500
TIME, msec

Fig. 2

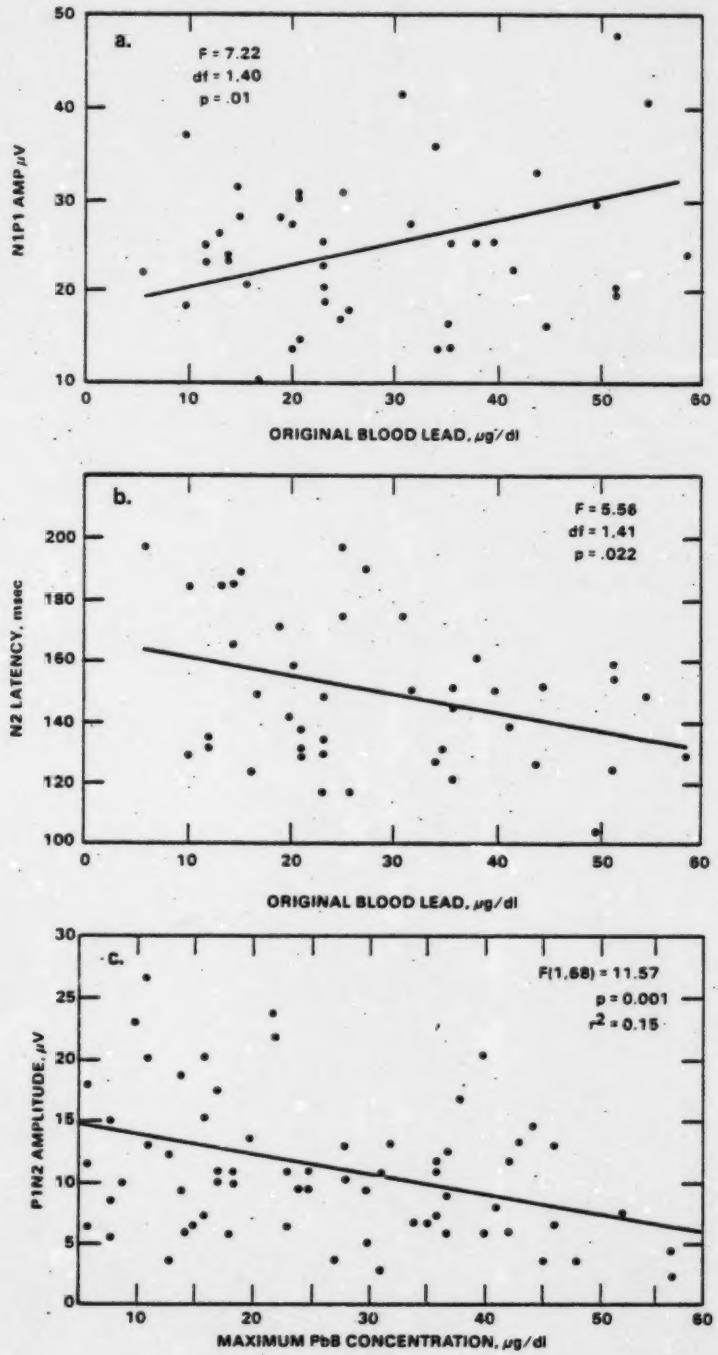
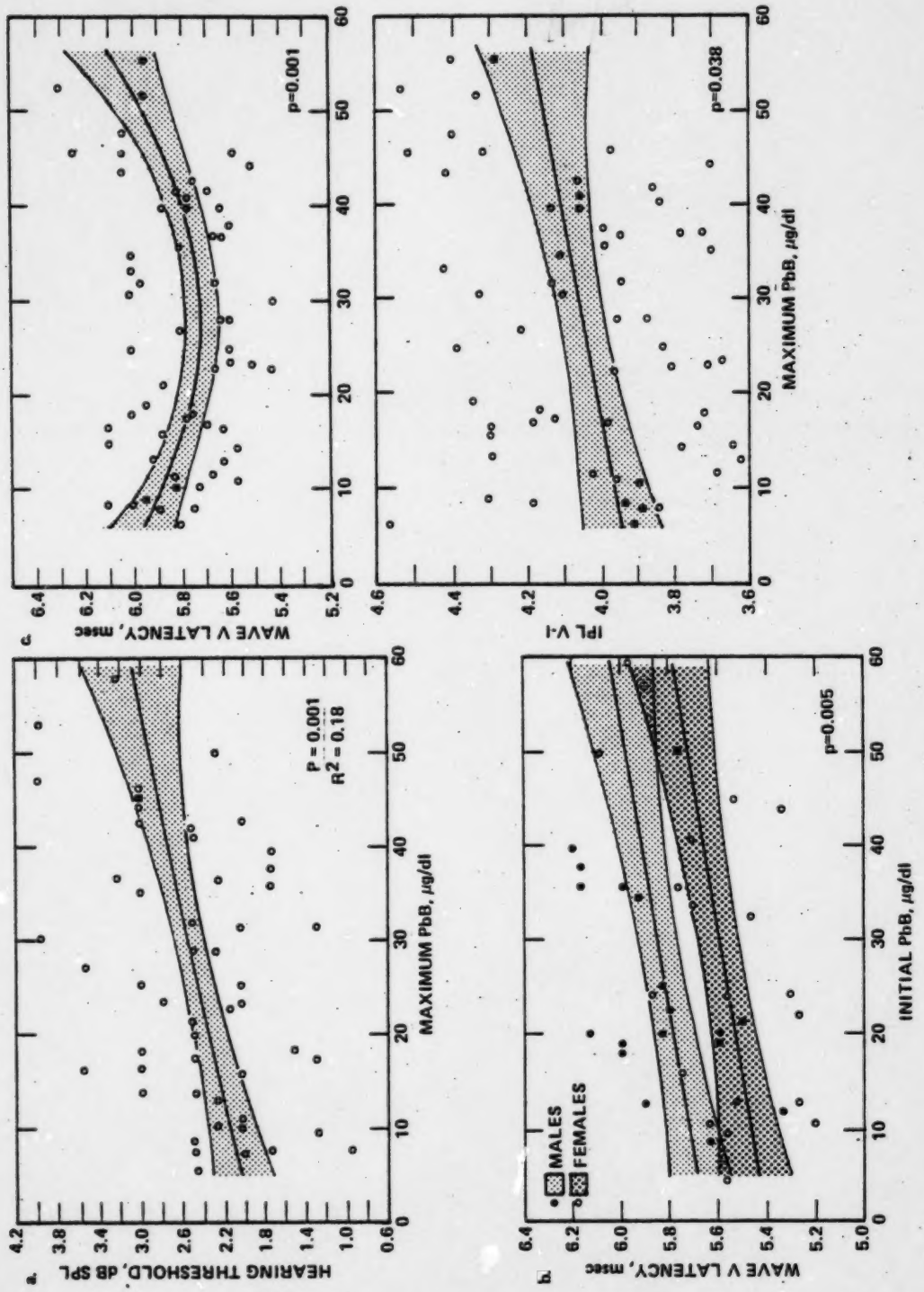

a.
F = 7.22
df = 1,40
p = .01
N1P1 AMP, μV
ORIGINAL BLOOD LEAD, μg/dl
b.
F = 5.56
df = 1,41
p = .022
N2 LATENCY, msec
ORIGINAL BLOOD LEAD, μg/dl
c.
F(1,68) = 11.57
p = 0.001
r² = 0.15
P1N2 AMPLITUDE, μV
MAXIMUM PbB CONCENTRATION, μg/dl

Fig 3


a.
HEARING THRESHOLD, dB SPL
P = 0.001
R^2 = 0.18
MAXIMUM PbB, µg/dl
b.
WAVE V LATENCY, msec
MALES
FEMALES
p=0.005
INITIAL PbB, µg/dl
c.
WAVE V LATENCY, msec
p=0.001
IPL V-I
p=0.038
MAXIMUM PbB, µg/dl